Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment of the insecticide Plenum 50 WG with the active substances pymetrozine

Opinion of VKM on plant protection products of the Norwegian Scientific Committee for Food Safety

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Summary

Plenum is a new insecticide containing the new active substance pymetrozine. Plenum is an insecticide against different pests in ornamentals, lettuce, cucumber and tomato in greenhouse and against pollen beetles in oilseed- and turnip rapes. The risk assessment was finalized at a meeting Mai 29, 2012, by VKM's Scientific Panel on plant protection products (VKM). The Panel is in particular asked by the Norwegian Food Safety Authority to look at the following:

- The human health risk for operators related to the properties of the active substance and the product. The Panel is in particular asked to look at the following:
    - The effects seen in studies on dog and if these effects warrant a classification for chronic toxicity.
    - The oncogenic effects in liver and lungs
    - The genotoxicity of metabolite CGA 300407.
    - The effects on reproduction and if the effects seen in teratology studies and developmental neurotoxicity study warrant a classification for developmental toxicity
    - The establishment of NOAELs and reference values (ADI, AOEL and ARfD).
    - The classification and labelling of the active substances and the product.

VKM's conclusion is as follows:

The effects reported in the repeated dose toxicity studies with dogs should be considered as adverse.

The increased incidence of liver and lung tumors should be considered as relevant for humans. It cannot be excluded that a genotoxic mechanism could be involved in the formation of the liver tumors, which would have implications for risk assessment. It should therefore be considered to test pymetrozine in more sensitive *in vivo* genotoxic endpoints in liver.

The effects reported in the teratogenicity studies in rats and rabbits and in the developmental neurotoxicity study in rats should be considered for a classification of pymetrozine for developmental toxicity.

Risk calculations with both the German model and the UK POEM show low risk if personal protection equipment is used.

VKM propose:

- NOAEL of 0.6 mg/kg bw/day for pymetrozine based on the 1-year study in dogs.
- AOEL of 0.006 mg/kg bw/day for pymetrozine based on the NOAEL value at 0.6 mg/kg bw/day from the one year study in dogs and an UF of 100.
- ADI of 0.006 for pymetrozine based on the NOAEL value at 0.6 mg/kg bw/day from the one year study in dogs and an UF of 100.
- ARfD of 0.02 mg/kg bw/day for pymetrozine based on the LOAEL value at 8.1 mg/kg bw/day from the developmental neurotoxicity study and an UF of 500 (10 x interspecies difference, 10 x intraspecies difference, 3 x due to the use of a LOAEL value and 2 x due to the adversity of the neurodevelopmental effects).

VKM supports the classification proposal from Norwegian Food Safety Authority.

Background

VKM performs risk assessments in the context of pesticide registration cf. Regulation on Pesticides § 4. The Norwegian Food Safety Authority, National Registration Section, is responsible for reviewing and evaluating the documentation submitted by the pesticide notifier. The Norwegian Food Safety Authority takes the final regulatory action regarding registration or deregistration of pesticides based on VKMs risk assessment, along with a comparative assessment of risk and benefits and the availability of alternatives (the principle of substitution).

The Norwegian Food Safety Authority submitted a request on April 20, 2012 for VKM to perform a risk assessment on use of the pesticide Plenum containing the active substance pymetrozine. The health risk assessments of the product were finalized by VKM in June, 2012.

Terms of reference

Plenum 50 WG is a new product containing the new active substance pymetrozine. The application is for use against different pests in ornamentals, lettuce, cucumber, and tomato in greenhouse, and against pollen beetles in oilseed- and turnip rapes.

The Norwegian Food Safety Authority would like, in this regard, an assessment of the following:

The human health risk for operators related to the properties of the active substance and the product. The Panel is in particular asked to look at the following:

- The effects seen in studies on dog and if these effects warrant a classification for chronic toxicity.
- The oncogenic effects in liver and lungs.
- The effects on reproduction and if the effects seen in teratology studies warrant a classification for developmental toxicity.
- The genotoxicity of metabolite CGA 300407.
- The establishment of NOAELs and reference values (ADI, AOEL and ARfD).
- The classification and labeling of the active substance and the product.

The Norwegian Food Safety Authority added to the terms of reference in an E-mail 7. May 2012 (in Norwegian):

“US EPA har vurdert et forsøk om “ Developmental Neurotoxicity (DNT)” som ikke var tilsendt Mattilsynet. Forsøket ble etterspurt og er nå innlevert. Forsøket er ikke standardkrav, men utføres når funn i standardforsøk tilsier at stoffet kan ha effekter på utviklingen av nervesystemet.

DNT forsøket med pymetrozin ble ikke vurdert i forbindelse med inkludering av virksomt stoff i EU. Mattilsynet viser til US EPAs vurdering av dette forsøkt (se vedlegg, side 8-9). Det er bl. a. konkludert med at stoffet gir morfologiske endringer i deler av hjernen hos avkom og at dette skjer ved doser som ikke påvirker moren. NOAEL kunne ikke fastsettes. En LOAEL på 8 mg/kg/dag ble fastsatt basert på morfologiske endringer i hjernen hos avkommet.

Faggruppen bes å vurdere om funn i dette forsøket gir en strengere klassifisering enn foreslått i vår rapport og om dette forsøket påvirker fastsettelsen av foreslåtte grenseverdier».

1 Background documentation

VKM's risk assessment is based on the Norwegian Food Safety Authority's evaluation (2012) of the documentation submitted by the applicant. The Norwegian Food Safety Authority publishes both their evaluation of Plenum and their final regulatory action on the registration of the pesticide product at their homepage (www.Mattilsynet.no)

2 Procedure

The first three steps of the risk assessment (hazard identification, hazard characterization and assessment of exposure) are performed by the Norwegian Food Safety Authority and involve an assessment of the documentation submitted by the pesticide notifier. The resulting report on hazard identification, hazard characterization and assessment of exposure, from which the summary is included in the present document, is then reviewed by VKM. This review may result in some amendments in the original documents of both the summary and the full report issued by the Norwegian Food Safety Authority (2012). The fourth step (risk characterization) is based on the three first steps and is VKM's conclusions or risk assessment.

2.1 HEALTH RISK ASSESSMENT

The assessment of health risk of pesticides is based on the adverse effects produced by the active substance and product in several experimental test systems including long term animal studies. On the basis of this, limits of exposure which represent no health risk are determined. The limits take account of the uncertainties of extrapolating data for animal to human. Then the limits are compared to the operator exposure and human exposure to possible residues in food.

The UKPoem and the German model estimate of exposure are used to estimate the operator exposure. The models are based on a limited number of studies and are not validated. Thus, the models may not always be sufficiently representative for Norwegian conditions. The limitations of model estimates of exposure are taken into consideration when the calculated level of exposure is close to the threshold limit for acceptable operator exposure (Acceptable Operator Exposure Level; AOEL). VKM uses the 75 percentile of exposure assessment for both UK poem and German model. VKM has to base their assessment on the models whenever exposure data for the product is not presented.

VKM makes use of a higher safety factor when calculating AOEL and ADI in cases where the product contains critical active substances with serious adverse inherent properties (toxic to reproduction or carcinogenic).

In order to describe the exceeding of maximum tolerated dose, VKM makes use of a scale. The scale is based on the ratio between the estimated exposure based on models or measured exposure in field studies and the Acceptable Operator Exposure Level (AOEL). In case the estimated exposure significantly exceeds AOEL, use of the products may lead to increased risk for health effects.

The following scale is used:

Very high excess of AOEL	more than 500% of the limit
High excess of AOEL	300 – 500% of the limit

Medium excess of AOEL 150-300% of the limit

Moderate excess of AOEL 100-150% of the limit

The limit is not exceeded

VKM may take into consideration critical co-formulants of the product when the degree of risk is to be determined. Consequently, if a product contains critical co-formulants it may be assessed to represent higher risk than what the inherent properties of active substances imply.

3 Summary by the Norwegian Food Safety Authority (hazard identification, hazard characterization and assessment of exposure)

Plenum 50 WG is a new product containing the new active substance pymetrozine. Pymetrozine was introduced in EU in 1993, and is approved for use till 31.12.2015. The formulation of Plenum 50 WG is water soluble granules (WG), containing 500 g/kg of the active substance. The application is for use against different pests in ornamentals, lettuce, cucumber, and tomato in greenhouse, and against pollen beetles in oilseed- and turnip rapes.

The effect mechanism of Plenum 50 WG differs from all insecticides known so far and also covers pests that are resistant against active substances used so far. Plenum 50 WG is an insecticide with a specific contact and feed effect against aphids and whiteflies. The insects stop sucking/eating immediately after intake of Plenum 50 WG, and the honey dew production is also quickly stopped.

Plenum 50 WG will play an important role in reducing risk of resistance development against the other insecticides registered for use against biting and sucking insects, particulary against neonicotinoids in aphids, and pyriproxifen in whiteflies. Plenum 50 WG is gentle against beneficials, except bees and bumblebees. For the turnip- and oil seed rape growers, Plenum 50 WG may be a useful product for managing pyretroid resistant pollen beetles.

In greenhouses, there is applied to use 120-720 g Plenum 50 WG /ha, depending on culture and pest, maximum 3 applications. Against pollen beetles in oilseed and turnip rapes it is recommended to use 150 g/ha, maximum 1 application.

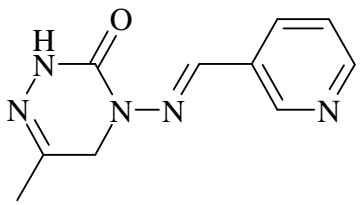
Based on the product's use against pollen beetles in turnip and oil seed rapes the standardized area dose is proposed set to 150 g Plenum 50 WG/ha (75 g pymetrozine/ha) corresponding 15 g /daa (7,5 g a.s/daa).

3.1 IDENTITY AND PHYSICAL/CHEMICAL DATA

Product name	Plenum 50 WG
Active substance	pymetrozine
Formulation	wettable granule
Concentration of active substance	500 g/kg
IUPAC-name	6-methyl-4-[(E)- (pyridin-3-ylmethylene)amino]-4,5-dihydro-2H -[1,2,4]-triazin-3one

CAS number 123312-89-0

Structural formula



Molecular weight	217.2	
Water solubility	High	270 g/l (25°C)
Vapour pressure	Low	< 4.2·10-6 Pa (25°C)
Henrys law const.	Low	< 3.0·10-6 Pa·m3/mol
log Pow	Low	-0.19
pKa		4.06

3.2 MAMMALIAN TOXICOLOGY

3.2.1 PYMETROZINE

3.2.1.1 *Toxicokinetics*

Absorption: Orally administered pymetrozine was rapidly and almost completely absorbed from the GI into the general circulation. The bioavailability of the oral dose was determined to be 0.9 for both sexes, demonstrating a high extent of absorption. At the high dose level, the extent of absorption was greater than at the low dose level. The difference in absorption at the high and low dose is assumed to be due to saturation of kinetic processes. In general, females of all dose groups had slightly higher total absorption values compared to males.

Distribution: Seven days after administration of radiolabelled pymetrozine, low but detectable residues were measured in all tissues and organs. Tissue residues of the pyridine label were 2 times to 70 times higher compared to the triazine label, and the highest amounts of residues were found in heart, skeletal muscle, kidneys, liver and brain.

Metabolism: A large number of metabolites were excreted in urine and faeces. Comparison patterns between different groups of rats revealed no qualitative dependence of sex, route of administration dose level and pre-treatment. The metabolism of pymetrozine consist of three major reactions: Oxidation reactions at the methyl substituent, oxidation reactions at the triazine-methylene group, and cleavage reactions between the triazine and the pyridine ring systems.

Excretion: Pymetrozine was rapidly and extensively excreted. The principle rout of excretion was urine. A higher renal excretion at the high dose level compared to the low dose level was seen. The pre-treated animals had slightly higher total excretion values compared to animals which had not been pre-treated, this was especially pronounced for males. Considerable amounts (12-30%) of pymetrozine were also excreted via biliary excretion.

3.2.1.2 *Acute toxicity*

Pymetrozine is of low acute toxicity after oral, dermal and inhalation exposure, and therefore no classification is required. Pymetrozine was not found to be neither a skin- or eye irritant nor a skin sensitizer.

3.2.1.3 *Genotoxicity*

All *in vitro* and *in vivo* genotoxicity studies were shown to be negative.

3.2.1.4 *Subchronic and chronic toxicity*

Several target organs were identified in the sub-chronic studies on dogs. Myopathy and anemia was observed in both the 90-day and 1-year study. Other findings included bile duct proliferation, hepatocyte necrosis, skeletal muscle atrophy, lymphocytic infiltration in several organs,inflammatory cell infiltration in the liver, increased haemosiderosis in liver and spleen, decreased testis weights and increased liver weights.

3.2.1.5 *Carcinogenicity*

Increased incidences of liver tumors were seen in chronic studies in mice and rats. There was also an increase in lung tumors in female mice.

The reporting member state (RMS) and the notifier argues that the observed increase in lung tumours is not related to the treatment with pymetrozine. The following argumentation is given: “There was no increase in the non-neoplastic prestage of lung tumours in mice. The incidences of lung tumours in male mice were comparable between all treated groups and the concurrent control group. There is no evidence that male mice are less sensitive to chemically-induced lung tumours than females. Therefore, the increased incidences of lung tumours in females cannot be unequivocally attributed to the application of the test substance”

The incidences of lung tumours in female mice are, however, above the historical control and are therefore believed to be treatment related.

It is also argued that the liver tumors are a result of a non-genotoxic mechanism as pymetrozine was not shown to be genotoxic in any of the performed genotoxicity tests. In addition, special studies show that biochemical and morphological changes seen in these studies correlate with liver tumors observed in in the chronic studies at same dose levels.

However, a clear mechanism of action is not demonstrated. The possibility of the liver tumors resulting from the genotoxicity of the metabolite CGA 300407 can therefore not be excluded.

3.2.1.6 *Reproductive toxicology and teratogenesis*

In the rat reproduction study, a decrease in parental and pups body weigh was observed. The decrease in the F2 pups body weigh seen from the first week of lactation and onwards indicates an effect of the substance through the milk. In the rabbit teratology study an increase in post-implantation loss was found. External anomalies and variations were increased. In the rat teratology study an increase in external and skeletal malformations and an increase in skeletal anomalies and variations were seen. Although these abnormalities were seen at doses causing maternal toxicity (reduced food intake and body weigh gain/body weigh loss), it is not possible to decide if these effects are secondary to the maternal toxicity.

3.2.1.7 *Neurotoxicity*

Neurotoxic effects were observed in the acute neurotoxicity study in the rat an included lower body temperature, FOB changes and decreased motor activity. In the subchronic neurotoxicity excessive head movement and sniffing were seen. The results from these studies show that that the nervous system is a target organ for pymetrozine

3.2.1.8 *Special studies*

Biochemical and morphological changes seen in these studies correlate with mice and rats liver tumors observed in in the chronic studies at same dose levels.

3.2.1.9 *Human data*

No data reported.

3.2.1.10 *Classification and labelling*

The proposed classification is Xn; Carc. Cat. 3, R40 (Possible risks of irreversible effects). Rep. Cat. 3, R63 (Possible risk of harm to unborn child).

3.2.1.11 *Reference values*

ADI

The ADI = 0.006 mg/kg/day is proposed to be based on one year dog study with a NOAEL = 0.6 mg/kg/day and UF of 100. The ADI in EU is based on an overall evaluation of the 90-day and one year studies on dog with an overall NOAEL of 3 mg/kg/day giving an ADI of 0.03 mg/kg/day and an UF of 100.

AOEL

The AOEL = 0.006 mg/kg/day is proposed to be based on one year dog study with a NOAEL = 0.6 mg/kg/day and UF of 100. The ADI in EU is based on an overall evaluation of the 90-day and one year studies on dog with an overall NOAEL of 3 mg/kg/day giving an ADI of 0.03 mg/kg/day and an UF of 100.

ARfD

The ARfD = 0.02 mg/kg/day for pymetrozine based on the LOAEL value at 8.1 mg/kg bw/day from the developmental neurotoxicity study and an UF of 500 (10 x interspecies difference, 10 x intraspecies difference, 3 x due to the use of a LOAEL value and 2 x due to the adversity of the neurodevelopmental effects).

3.2.2 METABOLITES

CGA 300407 is a metabolite identified as a rodent metabolite. It is also occurring in the environment and as a residue in plant and animal commodities. This metabolite is shown to be mutagenic *in vitro* and *in vivo*. The notifier considers the metabolite as an *in vivo* contact mutagen as positive result was seen in the Comet assay in the mouse forestomach, but not in the micronucleus test in the mouse bone marrow. The metabolite was however not tested in mammalian cells *in vitro* and not adequately tested *in vivo* in the liver. The notifier argues that the negative comet assay with pymetrozine provides a robust evaluation of the *in vivo* genotoxicity of the metabolite. However, a robust conclusion on the *in vivo* genotoxicity in the liver can only be drawn from further testing of the metabolite. A comet assay *in vivo* in the liver and an analysis of adduct formation or the use of transgenic rodents, should be carried out to clarify the *in vivo* mutagenicity of this metabolite.

3.2.3 CO-FORMULANTS

Plenum 50 WG does not contain co-formulants occurring above the limit that trigger labelling according according to Annex VI of CLP.

3.2.4 PLENUM 50 WG

3.2.4.1 *Acute toxicity*

Plenum 50 WG was not harmful by swallowing, skin contact or by inhalation. Plenum 50 WG is neither irritating to the eye and skin nor found to be a dermal sensitizer.

3.2.4.2 *Classification and labelling*

Plenum is proposed to labeled as Xn; Carc. Cat. 3, R40 (Possible risks of irreversible effects). Rep. Cat. 3,R63 (Possible risk of harm to unborn child).

3.2.4.3 *Dermal absorption*

A dermal absorption of 6 % for the formulated product and for the diluted product is used in the calculation of the exposure.

3.2.4.4 *Operator, worker and bystander exposure*

3.2.4.4.1 Operator exposure

AOEL is exceeded without using the PPE in both models. PPE (Gloves under mixing and loading+ A1P2 under mixing +coveralls and sturdy footwear under application) should be used for not exceeding the AOEL.

3.2.4.4.2 Re-entry and bystander exposure

Pymetrozine

AOEL is exceeded for worker harvesting ornamentals and vegetables without using PPE. The use of gloves and standard protective garment reduces the exposure bellow the AOEL.

Metabolite CGA 300407

The metabolite is found as residue in the plant metabolism studies. The notifier has submitted an exposure assessment, considering that this metabolite acts through a threshold process with the possibility to set an AOEL. The metabolite is however not sufficiently studied *in vivo* and a possible genotoxic effect cannot be ruled out. It is at the moment not possible to set an AOEL for this metabolite. A risk assessment for the metabolite CGA 300407 can not be performed as it is not sufficiently studied and a possible *in vivo* genotoxic effect cannot be ruled out.

3.2.5 RESIDUES IN FOOD OR FEED

Residues are not discussed in this report.

3.3 ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL EFFECTS

Environmental fate and ecotoxicological effects are not discussed in this report.

3.4 DOSSIER QUALITY AND COMPLETENESS

The submitted dossier is in accordance with the data requirements. The studies are conducted according to the OECD guidelines and are of acceptable quality.

4 Risk characterization

4.1 SUMMARY OF HUMAN TOXICITY/INHERENT PROPERTIES

In the terms of reference it was stated that VKM in particular should look at the following:

The Norwegian Food Safety Authority would like, in this regard, an assessment of the following:

The human health risk for operators related to the properties of the active substance and the product. The Panel is in particular asked to look at the following:

- The effects seen in studies on dog and if these effects warrant a classification for chronic toxicity.
- The oncogenic effects in liver and lungs.
- The genotoxicity of metabolite CGA 300407.
- The effects on reproduction and if the effects seen in teratology studies and in developmental Neurotoxicity (DNT) study warrant a classification for developmental toxicity.
- The establishment of NOAELs and reference values (ADI, AOEL and ARfD).
- The classification and labeling of the active substance and the product.

VKM discussed these points in-depth:

4.1.1 THE EFFECTS SEEN IN STUDIES ON DOG

From the summary (chapter 3.2.1.4) and the Norwegian Food Safety Authority's evaluation (2012):

"Several target organs were identified in the sub-chronic studies on dogs. Myopathy and anemia was observed in both the 90-day and 1-year study. Other findings included bile duct proliferation, hepatocyte necrosis, skeletal muscle atrophy, lymphocytic infiltration in several organs, inflammatory cell infiltration in the liver, increased haemosiderosis in liver and spleen, decreased testis weights and increased liver weights".

4.1.1.1 *The opinion of VKM*

Effects were reported in a 90 day and one year study in dogs. These effects included; severe anemia, adverse changes in haematology, hepatocellular necrosis, atrophy of the thymus, increased cholesterol levels, myopathy, and increased splenic and hepatic hemosiderosis. In males atrophy of testis and reduced spermatogenesis was reported as well. Some of these effects were present after the recovery period. Effects were reported from 14 mg/kg bw/day in the 90 days study and from 5 mg/kg bw/day in the one year study. The effects reported should be considered as adverse. The NOAEL from the one year study was 0.6 mg/kg bw/day and is used for deriving ADI and AOEL.

4.1.2 THE ONCOGENIC EFFECTS IN LIVER AND LUNGS

From the summary (chapter 3.2.1.5) and the Norwegian Food Safety Authority's evaluation (2012):

"Increased incidences of liver tumors were seen in chronic studies in mice and rats. There was also an increase in lung tumors in female mice.

The reporting member state (RMS) and the notifier argues that the observed increase in lung tumours is not related to the treatment with pymetrozine. The following argumentation is given: "There was no increase in the non-neoplastic prestage of lung tumours in mice. The incidences of lung tumours in male mice were comparable between all treated groups and the concurrent control group. There is no evidence that male mice are less sensitive to chemically-induced lung tumours than females. Therefore, the increased incidences of lung tumours in females cannot be unequivocally attributed to the application of the test substance"

The incidences of lung tumours in female mice are, however, above the historical control and are therefore believed to be treatment related.

It is also argued that the liver tumors are a result of a non-genotoxic mechanism as pymetrozine was not shown to be genotoxic in any of the performed genotoxicity tests. In addition, special studies show that biochemical and morphological changes seen in these studies correlate with liver tumors observed in in the chronic studies at same dose levels.

However, a clear mechanism of action is not demonstrated. The possibility of the liver tumors resulting from the genotoxicity of the metabolite CGA 300407 can therefore not be excluded".

4.1.3 THE GENOTOXICITY OF METABOLITE CGA 300407.

From the summary (chapter 3.2.2):

"CGA 300407 is a metabolite identified as a rodent metabolite. It is also occurring in the environment and as a residue in plant and animal commodities. This metabolite is shown to be mutagenic in vitro and in vivo. The notifier considers the metabolite as an in vivo contact mutagen as positive result was seen in the Comet assay in the mouse forestomach, but not in the micronucleus test in the mouse bone marrow. The metabolite was however not tested in mammalian cells in vitro and not adequately tested in vivo in the liver. The notifier argues that the negative comet assay with pymetrozine provides a robust evaluation of the in vivo genotoxicity of the metabolite. However, a robust conclusion on the in vivo genotoxicity in the liver can only be drawn from further testing of the metabolite. A comet assay in vivo in the liver and an analysis of adduct formation or the use of transgenic rodents, should be carried out to clarify the in vivo mutagenicity of this metabolite".

4.1.3.1 *The opinion of VKM*

Exposure to pymetrozine resulted in increased incidences of liver tumours in female rats that were above the historical control data (HCD) and in male and female mice. An increase in lung adenoma plus carcinoma was reported in female mice that were above the HCD.

Several arguments are presented to suggest that the tumors observed are unrelated to the exposure to pymetrozine. VKM has however not been convinced by these arguments, and have the opinion that it cannot be excluded that the observed tumors are relevant to human exposure.

A central question is whether the tumors result from a non-genotoxic mechanism, considering that pymetrozine has not been shown to be genotoxic. A complicating finding is however that of a genotoxic metabolite, CGA 300407.

The metabolite CGA 300407 gave positive response *in vitro* for chromosomal aberrations in CHO cells and human lymphocytes, and *in vivo* in a Comet assay in mouse forestomach. It is argued that the metabolite could be considered as a locally acting genotoxin in the forestomach, and thus not be involved in the formation of the liver tumors. However, the metabolite may also be formed by direct transformation of the mother substance in the liver.

It is the opinion of VKM that it cannot be excluded that a genotoxic mechanism could be involved in the formation of the liver tumors, which would have implications for risk assessment. It should therefore be considered to test pymetrozine in more sensitive *in vivo* genotoxic endpoints in liver.

4.1.4 THE EFFECTS ON REPRODUCTION

From the summary (chapter 3.2.1.6):

"In the rat reproduction study, a decrease in parental and pups body weigh was observed. The decrease in the F2 pups body weigh seen from the first week of lactation and onwards indicates an effect of the substance through the milk. In the rabbit teratology study an increase in post-implantation loss was found. External anomalies and variations were increased. In the rat teratology study an increase in external and skeletal malformations and an increase in skeletal anomalies and variations were seen. Although these abnormalities were seen at doses causing maternal toxicity (reduced food intake and body weight gain/body weight loss), it is not possible to decide if these effects are secondary to the maternal toxicity".

4.1.4.1 *The opinion of VKM*

No effects on reproductive parameters were reported in a 2-generation study in rats. A dose-depended increase in early resorptions was reported in a teratology study in rabbits. In repeated dose toxicity studies in rats reduced spermatogenesis and reduced spermatozoa in epididymis was reported. In dogs reduced testes weight, minimal atrophy of the testis as well as atrophy of prostatic glandular tissue was reported as well. These effects could be considered relevant for humans.

In a teratology study in rats increase in external abnormalities and skeletal malformations that was above the historical control data was reported. Maternal effects included a significant reduced body weight. In a teratogenicity study in rabbits a dose-depended increase in post-implantation loss was reported and one dam aborted and 3 dams resorbed litters completely. External anomalies were significantly increased and were above the historical control data. Maternal toxicity was evident as significantly reduced body weight gain. It cannot be excluded that the abnormalities reported in the pups and the increase in post-implantation loss could be secondary to maternal toxicity.

In a rat developmental neurotoxicity study changes in brain morphometry were reported in pups including increased thickness of the corpus callosum and inner granular and molecular layers of the pre-pyramidal fissure in the cerebellum in males at pnd 63 and dorsal cortex in females at pnd 12. All dams in the high dose group were sacrificed prior to scheduled termination due to clinical signs of toxicity and complete litter losses. Changes in brain morphometry were reported in the absence of maternal toxicity and are considered as an

adverse effect in pups. The LOAEL from this study was 8.1 mg/kg bw/day and is used for deriving ARfD.

In the 2-generation study in rats a decrease in pup weight was reported from the second week of lactation in F1 and from the first week of lactation in F2. The data gives no information if the decrease in pup body weight was related to exposure to Pymetrozine from milk, or is related to decreased milk production by the dams. Since pups starts to eat around this time it is also difficult to conclude if the decrease in pup weight is related to direct exposure to Pymetrozien from food.

VKM concluded that the effects reported in the teratogenicity studies in rats and rabbits and in the developmental neurotoxicity study in rats should be considered for a classification of pymetrozine for developmental toxicity.

4.1.5 ESTABLISHMENT OF REFERENCE VALUES:

NOAEL

EU has proposed a NOAEL of 3 mg/kg bw/day for calculation of ADI and AOEL. The Norwegian Food Safety Authority proposes a NOAEL of 0.6 mg/kg bw/d from the study with one-year diet study with dog.

VKM support an NOAEL of 0.6 mg/kg bw/day for pymetrozine based on the 1-year study in dogs.

ADI

An ADI of 0.006 mg/kg bw/day is proposed to be based on one year dog study with a NOAEL = 0.6 and UF=100.

The ADI in EU is based on an overall evaluation of the 90-day and one year studies on dog with an overall NOAEL of 3 mg/kg/day giving an ADI of 0.03 mg/kg/day and an UF of 100.

VKM support an ADI of 0.006 mg/kg bw/day for pymetrozine based on the NOAEL value at 0.6 mg/kg bw/day from the one year study in dogs and an UF of 100.

AOEL

0.006 mg/kg bw/day is proposed to be based on one year dog study with a NOAEL = 0,6 and UF=100.

The AOEL in EU is based on an overall evaluation of the 90-day and one year studies on dog with an overall NOAEL of 3 mg/kg/day giving an ADI of 0.03 mg/kg/day and an UF of 100.

The metabolite CGA 300407

The metabolite is found as residue in the plant metabolism studies. The notifier has submitted an exposure assessment, considering that this metabolite acts through a threshold process with the possibility to set an AOEL. The metabolite is however not sufficiently studied *in vivo* and a possible genotoxic effect cannot be ruled out. It is at the moment not possible to set an AOEL for this metabolite. A risk assessment for the metabolite CGA 300407 cannot be performed as it is not sufficiently studied and a possible *in vivo* genotoxic effect cannot be ruled out.

VKM support an AOEL of 0.006 mg/kg bw/day for pymetrozine based on the NOAEL value at 0.6 mg/kg bw/day from the one year study in dogs and an UF of 100.

ARfD

The ARfD = 0.1 mg/kg is proposed to be based on rat teratology study with a NOAEL = 10 mg/kg/day and UF = 100. This is the same ARfD as in EU.

VKM proposes an ARfD of 0.02 mg/kg bw/day for pymetrozine based on the LOAEL value at 8.1 mg/kg bw/day from the developmental neurotoxicity study and an UF of 500 (10 x interspecies difference, 10 x intraspecies difference, 3 x due to the use of a LOAEL value and 2 x due to the adversity of the neurodevelopmental effects).

4.1.6 THE CLASSIFICATION AND LABELLING OF THE ACTIVE SUBSTANCE AND THE PRODUCT.

Plenum is proposed to be labeled as Xn; Carc. Cat. 3, R40 (Possible risks of irreversible effects). Rep. Cat. 3, R63 (Possible risk of harm to unborn child).

VKM supports the classification proposal from Norwegian Food Safety Authority.

4.2 HEALTH RISK CHARACTERIZATION

Health risk due to human exposure

VKM has based their risk characterization for operators on the summary from Norwegian Food Safety Authority presented in section 5.3 and on the exposure- and dose-response assessments presented in section 5.2.1 by applying the scale of exceed of AOEL.

Operator, worker and bystander exposure

Operator exposure
AOEL is exceeded without using the PPE in both models. PPE (Gloves under mixing and loading+ A1P2 under mixing +coveralls and sturdy footwear under application) should be used for not exceeding the AOEL.

Re-entry and bystander exposure
AOEL is exceeded for worker harvesting ornamentals and vegetables without using PPE. The use of gloves and standard protective garment reduces the exposure bellow the AOEL.

Health risk due to residues in products for consumption
Not included in the terms of reference.

4.2.1 QUALITY OF THE SUBMITTED DOCUMENTATION

VKM is of the opinion that the documentation submitted to VKM is adequate as a basis for an evaluation of the active substance, the metabolites, and for the technical material.

5 Conclusion

The effects reported in the repeated dose toxicity studies with dogs should be considered as adverse.

The increased incidence of liver and lung tumours should be considered as relevant for humans. It is the opinion of VKM that it cannot be excluded that a genotoxic mechanism could be involved in the formation of the liver tumors, which would have implications for risk assessment. It should therefore be considered to test pymetrozine for more sensitive *in vivo* genotoxic endpoints in liver.

VKM concluded that the effects reported in the teratogenicity studies in rats and rabbits and in the developmental neurotoxicity study in rats should be considered for a classification of pymetrozine for developmental toxicity.

VKM proposes:

- NOAEL of 0.6 mg/kg bw/day for pymetrozine based on the 1-year study in dogs.
- AOEL of 0.006 mg/kg bw/day for pymetrozine based on the NOAEL value at 0.6 mg/kg bw/day from the one year study in dogs and an UF of 100.
- ADI of 0.006 for pymetrozine based on the NOAEL value at 0.6 mg/kg bw/day from the one year study in dogs and an UF of 100.
- ARfD of 0.02 mg/kg bw/day for pymetrozine based on the LOAEL value at 8.1 mg/kg bw/day from the developmental neurotoxicity study and an UF of 500 (10 x interspecies difference, 10 x intraspecies difference, 3 x due to the use of a LOAEL value and 2 x due to the adversity of the neurodevelopmental effects).

VKM supports the classification proposal from Norwegian Food Safety Authority.

Risk calculations with both the German model and the UK POEM show low risk if personal protection equipment is used.

Attachment

Attached is The Norwegian Food Safety Authority's evaluation of the documentation submitted by the applicant, folowing application for registration of the insecticide Plenum (www.Mattilsynet.no)